



Research Institute for Fragrance Materials, Inc.

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June 15, 2007

Dr. William S. Stokes
NICEATM Director
NIEHS
P.O. Box 12233
MD EC-17
Research Triangle Park, NC 27709

Dear Dr. Stokes:

This letter is in response to the NICEATM request for data on the murine local lymph node assay that appeared in the Federal Register on Thursday May 17, 2007 (Volume 72, No. 95, p. 27815).

The Research Institute for Fragrance Materials, Inc. (RIFM), the international scientific authority for the safe use of fragrance materials, is the most comprehensive source of toxicology data, literature and information on the safety evaluation of fragrance materials. Through extensive research and testing and constant monitoring of all scientific literature available, RIFM maintains a database of fragrance and flavor materials considered the largest repository of this type of information in the world. All of RIFM's scientific findings are evaluated by an independent, scientific Expert Panel—an international group of dermatologists, pathologists, toxicologists and environmental scientists who are completely unbiased with no connection to the fragrance industry. More information about RIFM can be found on the RIFM web site at www.rifm.org.

The murine Local Lymph Node Assay (LLNA) has provided toxicologists with a tool that provides both a reduction in the use of animals and a refinement over traditional assays for hazard identification and potency classification of contact sensitizers. Since 2000, RIFM has used the LLNA almost exclusively for this purpose. The data that RIFM has generated in the LLNA has been incorporated into several publications that aim to provide a standardized data set for the development of alternative methodologies.

RIFM has explored the use of the LLNA in various essential oils. Mr. Jon Lalko, RIFM Senior Test Program Specialist managed this project, which had two goals: 1) to investigate the potential of individual essential oils to induce dermal sensitization and to determine the relative potency of the oil; and 2) to examine any difference in sensitization potential for the major components arising from their exposure. The initial work was published in *Food and Chemical Toxicology* (2007), Volume 44, pp. 739-746). A copy of the publication is attached. RIFM has continued to investigate the use of the LLNA in various essential oils. Enclosed is a summary of the LLNA data RIFM has sponsored on several essential oils.

Much work has been done to correlate the dose-response data obtained in the mouse LLNA with what is known about potency in humans. The EC3 value has recently been demonstrated to closely correlate with the NOEL from human sensitization tests designed to confirm lack of induction. RIFM has compared the relationship between the LLNA EC3 value and the NOEL for sensitization in humans. A detailed analysis of the dermal sensitization data for 31 fragrance ingredients that have exhibited dermal sensitization potential revealed that for the majority of the materials, there is a very good correlation between the EC3 or predicted NOEL from the LLNA and the NOEL in confirmatory human tests. This preliminary analysis was presented at the World Health Organization/International Program On Chemical Safety International Workshop On Skin Sensitization In Chemical Risk Assessment last October. The abstract, which is in press, is attached.

We hope that these data are useful. If there is any more information or details that we can provide, please feel free to contact me.

Best regards.

Sincerely,



Anne Marie Api, Ph.D.
Vice President,
Human Health Sciences

AMA/caj

cc: Jon F. Lalko
Ladd W. Smith